IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, ADRIAN PAUL BROWN, M.A., M.I.L., M.I.T.I., declare

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 5 Gilbert Road, London, SE11 4NZ.

2. That I am well acquainted with the French and English languages.

3. That the attached is a true translation into the English language of the certified copy of French Patent Application No. 00 08793 filed on 6th July 2000.

4. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

DECLARED THIS 14th DAY OF NOVEMBER 2002

A. P. Brown

A P BROWN

F R E N C H R E P U B L I C

INPI

NATIONAL INSTITUTE
FOR INDUSTRIAL
PROPERTY

PATENT OF INVENTION

UTILITY CERTIFICATE - CERTIFICATE OF ADDITION

OFFICIAL COPY

The Director General of the National Institute for Industrial Property certifies that the attached document is the true certified copy of an application for an Industrial Property Right filed at the Institute.

Issued in Paris, 11 OCT. 2002

For the Director General of the
National Institute for Industrial Property,
The Head of the Patents Department

(signature)

Martine PLANCHE

NATIONAL
INSTITUTE FOR
INDUSTRIAL
PROPERTY

NATIONAL PUBLIC INSTITUTION

HEAD OFFICE
26 bis, rue de Saint Petersbourg
75800 PARIS cedex 08
Telephone: 33 (1) 53 04 53 04
Facsimile: 33 (1) 42 93 59 30
www.inpi.fr
CREATED BY LAW NO. 51-444 OF 19th APRIL 1951

INPI

National
Institute for
Industrial Property
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 94 86 54

PATENT OF INVENTION
UTILITY CERTIFICATE

Intellectual Property Code - Book VI

cerfa
No. 11354*1

REQUEST FOR GRANT 1/2

Reserved for INPI

This form is to be completed legibly in black ink DB 540 W /260899

DEPOSITION OF DOCUMENTS **DATE 6 JULY 2000** **PLACE 75 INPI PARIS** **NATIONAL REGISTRATION NO. GIVEN BY THE INPI 0008793** **FILING DATE GIVEN BY THE INPI 06 JULY 2000**	**1 NAME AND ADDRESS OF THE APPLICANT OR OF THE AUTHORISED AGENT TO WHOM CORRESPONDENCE MUST BE ADDRESSED** ADIR ET COMPAGNIE 1, rue Carle Hébert 92415 COURBEVOIE Cedex
Your references for this file *(optional)* 9490 F1	
Confirmation of a deposit by facsimile	☐ No. given by INPI to the facsimile

2 NATURE OF THE APPLICATION	**Mark one of the following 4 boxes**	
Patent application	☒	
Application for a Utility Certificate	☐	
Divisional application	☐	
Initial patent application	No.	Date
or initial utility certificate application	No.	Date
Conversion of a European Patent Application	☐	
Initial patent application	No.	Date

3 TITLE OF THE INVENTION (maximum 200 characters or spaces)

New α crystalline form of perindopril tert-butylamine salt, a process for its preparation and pharmaceutical compositions containing it

4 DECLARATION OF PRIORITY OR REQUEST FOR THE BENEFIT OF THE FILING DATE OF A PRIOR FRENCH APPLICATION	Country or organisation Date No. Country or organisation Date No. Country or organisation Date No. ☐ **If there are other priorities, mark the box and use the "Continuation" form**

5 APPLICANT		☐ **If there are other Applicants, mark the box and use the "Continuation" form**	
Surname or company name		ADIR ET COMPAGNIE	
Forenames			
Legal nature			
SIREN No.			
APE-NAF Code			
Address	Street	1, rue Carle Hébert	
	Postal code and town	92415	COURBEVOIE Cedex
Country		FRANCE	
Nationality		FRENCH	
Telephone no. *(optional)*		01.55.72.60.00	
Facsimile no. *(optional)*		01.55.72.72.13	
E-mail address *(optional)*			

INPI

National
Institute for
Industrial Property

PATENT OF INVENTION
UTILITY CERTIFICATE

REQUEST FOR GRANT 2/2

Reserved for INPI

DEPOSITION OF DOCUMENTS
DATE **06 JULY 2000**
PLACE **75 INPI PARIS**
NATIONAL REGISTRATION NO. GIVEN BY THE INPI **0008793**

DB 540 W /260899

Your references for this file: *(optional)*		9490 F1	
6 AUTHORISED AGENT			
Surname		JAGUELIN-GUINAMANT	
Forename		Sylvie	
Practice or company		ADIR ET COMPAGNIE	
No. of standing power of attorney and/or of contractual bond			
Address	Street	1, rue Carle Hébert	
	Postal code and town	92415	COURBEVOIE Cedex
Telephone no. *(optional)*		01.55.72.60.00	
Facsimile no. *(optional)*		01.55.72.72.13	
E-mail address *(optional)*			
7 INVENTOR(S)			
The inventors are the Applicants		☐ Yes ☒ No **In this case, supply a separate designation of inventorship**	
8 SEARCH REPORT		**For a patent application only (including division and conversion)**	
immediate drawing up		☒	
or deferred drawing up		☐	
Payment of the fees in instalments		**Payment in three instalments, for natural persons only** ☐ Yes ☐ No	
9 REDUCTION IN FEES		**For natural persons only** ☐ Requested for the first time for this invention *(attach a notice of non-imposition)* ☐ Requested prior to this deposit *(attach a copy of the admissibility decision for this invention or indicate its reference)*	
If you have used the "Continuation" form, indicate the number of pages attached			

10 SIGNATURE OF THE APPLICANT OR OF THE AUTHORISED AGENT (Name and position of signatory) (signature)	**STAMP OF THE PREFECTURE OR OF THE INPI**
Sylvie JAGUELIN-GUINAMANT Patent Engineer	P. BERNOUIS (signature)

Law No. 78-17 of 6 January 1978 relating to information processing, data files and rights applies to the responses made on this form. It guarantees right of access to and correction of the data concerning you at the INPI.

INPI

National
Institute for
Industrial Property

PATENTS DEPARTMENT
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 93 59 30

PATENT OF INVENTION
UTILITY CERTIFICATE

Intellectual Property Code - Book VI

cerfa
No. 11235*02

DECLARATION OF INVENTORSHIP

Page No. 1 / 2

(if the applicant is not the inventor or not the only inventor)

This form is to be completed legibly in black ink DB 113 W /260899

Your references for this file *(optional)*	9490 F1
NATIONAL REGISTRATION NO.	0008793

TITLE OF THE INVENTION (maximum 200 characters or spaces)

New α crystalline form of perindopril tert-butylamine salt, a process for its preparation and pharmaceutical compositions containing it

APPLICANT(S):

ADIR ET COMPAGNIE
1, rue Carle Hébert
92415 COURBEVOIE Cedex

DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).

Surname		PFEIFFER	
Forenames		Bruno	
Address	Street	47, rue Ernest Renan	
	Postal code and town	95320	SAINT LEU LA FORET
Belonging company *(optional)*			
Surname		GINOT	
Forenames		Yves-Michel	
Address	Street	8, quai Saint-Laurent	
	Postal code and town	45000	ORLEANS
Belonging company *(optional)*			
Surname		COQUEREL	
Forenames		Gérard	
Address	Street	192, rue de l'Eglise	
	Postal code and town	76520	BOOS
Belonging company *(optional)*			

DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory)	Courbevoie, 6th July 2000
(signature)	
Sylvie JAGUELIN-GUINAMANT	
Patent Engineer	

INPI

National
Institute for
Industrial Property

PATENTS DEPARTMENT
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 93 59 30

PATENT OF INVENTION
UTILITY CERTIFICATE
Intellectual Property Code - Book VI

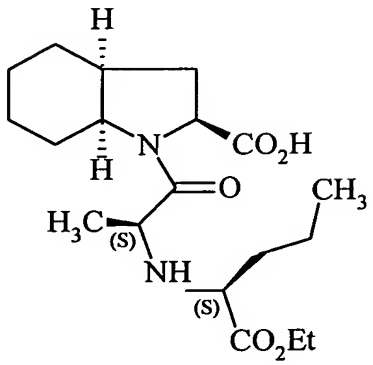
cerfa
No. 11235*02

DECLARATION OF INVENTORSHIP
Page No. 2 / 2
(if the applicant is not the inventor or not the only inventor)

This form is to be completed legibly in black ink DB 113 W /260899

Your references for this file *(optional)*		9490 F1	
NATIONAL REGISTRATION NO.		0008793	
TITLE OF THE INVENTION (maximum 200 characters or spaces)			
New α crystalline form of perindopril tert-butylamine salt, a process for its preparation and pharmaceutical compositions containing it			
APPLICANT(S):			
ADIR ET COMPAGNIE 1, rue Carle Hébert 92415 COURBEVOIE Cedex			
DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).			
Surname		BEILLES	
Forenames		Stéphane	
Address	Street	35, place de la Basse Vieille Tour	
	Postal code and town	76000	ROUEN
Belonging company *(optional)*			
Surname			
Forenames			
Address	Street		
	Postal code and town		
Belonging company *(optional)*			
Surname			
Forenames			
Address	Street		
	Postal code and town		
Belonging company *(optional)*			
DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory) (signature) Sylvie JAGUELIN-GUINAMANT Patent Engineer		Courbevoie, 6th July 2000	

The present invention relates to a new α crystalline form of perindopril tert-butylamine salt of formula (I) :



. $tBuNH_2$ (I),

to a process for its preparation and to pharmaceutical compositions containing it.

Perindopril and its pharmaceutically acceptable salts, and more especially its tert-butylamine salt, have valuable pharmacological properties.

Their principal property is that of inhibiting angiotensin I converting enzyme (or kininase II), which prevents, on the one hand, conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the other hand, degradation of bradykinin (a vasodilator) to an inactive peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular diseases, more especially in arterial hypertension and heart failure.

Perindopril, its preparation and its use in therapeutics have been described in European Patent specification EP 0 049 658.

In view of the pharmaceutical value of this compound, it has been of prime importance to obtain it with excellent purity. It has also been important to be able to synthesise it by means of a process that can readily be converted to the industrial scale, especially in a form that allows rapid filtration and drying. Finally, that form had to be perfectly reproducible, easily formulated and sufficiently stable to allow its storage for long periods without particular requirements for temperature, light, humidity or oxygen level.

The patent specification EP 0 308 341 describes an industrial synthesis process for perindopril. However, that document does not specify the conditions for obtaining perindopril in a form that exhibits those characteristics in a reproducible manner.

The Applicant has now found that a particular salt of perindopril, the tert-butylamine salt, can be obtained in a well defined, perfectly reproducible crystalline form that especially exhibits valuable characteristics of filtration, drying and ease of formulation.

More specifically, the present invention relates to the α crystalline form of the compound of formula (I), characterised by the following powder X-ray diffraction diagram, measured using a Siemens D5005 diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage of the most intense ray) :

Angle 2 theta (°)	**Inter-planar distance d (Å)**	**Intensity**	**Relative intensity (%)**
7.680	11.50	390	8.8
8.144	10.85	230	5.2
9.037	9.78	4410	100
10.947	8.08	182	4.1
13.150	6.73	82	1.9
13.687	6.46	83	1.9
14.627	6.05	582	13.2
15.412	5.74	770	17.5
16.573	5.34	1115	25.3
17.357	5.10	340	7.7
18.109	4.89	193	4.4
19.922	4.45	306	6.9
20.609	4.31	375	8.5
21.412	4.15	226	5.1
21.832	4.07	217	4.9
22.158	4.01	483	11
22.588	3.93	386	8.8
23.323	3.81	107	2.4
24.200	3.67	448	10.2
24.727	3.60	137	3.1
25.957	3.43	125	2.8

26.932	3.31	75	1.7
27.836	3.20	197	4.5
28.966	3.08	129	2.9
29.213	3.05	117	2.7

The invention relates also to a process for the preparation of the α crystalline form of the compound of formula (I), which process is characterised in that a solution of perindopril tert-butylamine salt in ethyl acetate is heated at reflux and is cooled gradually until crystallisation is complete.

- In the crystallisation process according to the invention it is possible to use the compound of formula (I) obtained by any process. Advantageously, the compound of formula (I) obtained by the preparation process described in patent specification EP 0 308 341 is used.

- The concentration of the compound of formula (I) in the ethyl acetate is preferably from 70 to 90 g/litre.

- Advantageously, the solution of the compound of formula (I) in ethyl acetate at reflux is first cooled to a temperature of from 55 to 65°C at a rate of from 5 to 10°C/hour, preferably from 6 to 8°C/hour, and then to ambient temperature.

- The solution can advantageously be seeded during the cooling step at a temperature of from 76 to 65°C.

- The perindopril tert-butylamine salt that is thereby obtained is in the form of individual needles about 0.2 mm long. That homogeneous distribution has the advantage of allowing especially rapid and efficient filtration and drying, as well as allowing the preparation of pharmaceutical formulations having a uniform and reproducible composition, which is especially advantageous when those formulations are intended for oral administration.

- The form thereby obtained is sufficiently stable to allow its storage for long periods without particular requirements for temperature, light, humidity or oxygen level.

The invention relates also to pharmaceutical compositions comprising as active ingredient the α crystalline form of the compound of formula (I) together with one or more appropriate, inert, non-toxic excipients. Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions etc..

The useful dosage can be varied according to the nature and severity of the disorder, the administration route and the age and weight of the patient. It varies from 1 to 500 mg per day in one or more administrations.

The pharmaceutical compositions according to the invention may also comprise a diuretic such as indapamide.

The following Examples illustrate the invention but do not limit it in any way.

The powder X-ray diffraction spectrum was measured under the following experimental conditions :

- Siemens D5005 diffractometer, scintillation detector,
- copper anticathode (λ=1.5405 Å), voltage 40 kV, intensity 40 mA,
- mounting θ-θ,
- measurement range : 5° to 30°,
- increment between each measurement : 0.02°,
- measurement time per step : 2 s,
- variable slits : v6,
- filter Kβ (Ni),
- no internal reference,

- zeroing procedure using the Siemens slits,
- experimental data processed using EVA software (version 5.0).

EXAMPLE 1 : α crystalline form of perindopril tert-butylamine salt

125 g of perindopril tert-butylamine salt obtained according to the process described in patent specification EP 0 308 341 are dissolved in 1.68 litres of ethyl acetate heated at reflux.

The temperature of the solution is then brought to 60°C in the course of 2 hours 30 minutes and is then cooled to ambient temperature.

The solid obtained is collected by filtration.

Powder X-ray diffraction diagram :

The powder X-ray diffraction profile (diffraction angles) of the α form of perindopril tert-butylamine salt is given by the significant rays collated in the following table together with the intensity and relative intensity (expressed as a percentage of the most intense ray).

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
7.680	11.50	390	8.8
8.144	10.85	230	5.2
9.037	9.78	4410	100
10.947	8.08	182	4.1
13.150	6.73	82	1.9
13.687	6.46	83	1.9
14.627	6.05	582	13.2
15.412	5.74	770	17.5
16.573	5.34	1115	25.3
17.357	5.10	340	7.7
18.109	4.89	193	4.4
19.922	4.45	306	6.9
20.609	4.31	375	8.5
21.412	4.15	226	5.1
21.832	4.07	217	4.9
22.158	4.01	483	11

22.588	3.93	386	8.8
23.323	3.81	107	2.4
24.200	3.67	448	10.2
24.727	3.60	137	3.1
25.957	3.43	125	2.8
26.932	3.31	75	1.7
27.836	3.20	197	4.5
28.966	3.08	129	2.9
29.213	3.05	117	2.7

EXAMPLE 2 : Pharmaceutical composition

Preparation formula for 1000 tablets each containing 4 mg of active ingredient :

Compound of Example 1 ..... 4 g

Hydroxypropylcellulose ..... 2 g

Wheat starch ..... 10 g

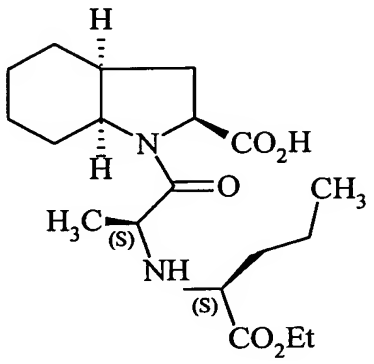
Lactose ..... 100 g

Magnesium stearate ..... 3 g

Talc ..... 3 g

CLAIMS

1. α crystalline form of the compound of formula (I) :



. $tBuNH_2$ (I),

characterised by the following powder X-ray diffraction diagram, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distances d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage with respect to the most intense ray) :

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
7.680	11.50	390	8.8
8.144	10.85	230	5.2
9.037	9.78	4410	100
10.947	8.08	182	4.1
13.150	6.73	82	1.9
13.687	6.46	83	1.9
14.627	6.05	582	13.2
15.412	5.74	770	17.5
16.573	5.34	1115	25.3
17.357	5.10	340	7.7
18.109	4.89	193	4.4
19.922	4.45	306	6.9
20.609	4.31	375	8.5
21.412	4.15	226	5.1
21.832	4.07	217	4.9
22.158	4.01	483	11

22.588	3.93	386	8.8
23.323	3.81	107	2.4
24.200	3.67	448	10.2
24.727	3.60	137	3.1
25.957	3.43	125	2.8
26.932	3.31	75	1.7
27.836	3.20	197	4.5
28.966	3.08	129	2.9
29.213	3.05	117	2.7

2. Process for the preparation of the α crystalline form of the compound of formula (I) according to claim 1, characterised in that a solution of perindopril tert-butylamine salt in ethyl acetate is heated at reflux and is then cooled gradually until crystallisation is complete.

3. Process according to claim 2, characterised in that the compound of formula (I) obtained by the preparation process described in patent specification EP 0 308 341 is used.

4. Process according to either claim 2 or claim 3, characterised in that the concentration of the compound of formula (I) in the ethyl acetate is from 70 to 90 g/litre.

5. Process according to any one of claims 2 to 4, characterised in that the solution of the compound of formula (I) in ethyl acetate at reflux is first cooled to a temperature of from 55 to 65°C at a rate of from 5 to 10°C/hour, and then to ambient temperature.

6. Process according to any one of claims 2 to 4, characterised in that the solution of the compound of formula I in ethyl acetate is seeded during the cooling step at a temperature of from 76 to 65°C.

7. Process according to claim 5, characterised in that the solution of the compound of formula (I) in ethyl acetate at reflux is first cooled to a temperature of from 55 to 65°C at a rate of from 6 to 8°C/hour, and then to ambient temperature.

8. Process according to any one of claims 2 to 7, characterised in that the perindopril tert-butylamine salt that is thereby obtained is in the form of readily filterable individual needles.

9. Pharmaceutical composition comprising as active ingredient the compound according to claim 1, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

10. Pharmaceutical composition according to claim 9 for use in the manufacture of medicaments for use as inhibitors of angiotensin I converting enzyme.

11. Pharmaceutical composition according to claim 10 for use in the manufacture of medicaments for use in the treatment of cardiovascular diseases.

12. Pharmaceutical composition according to any one of claims 9 to 11, characterised in that it also comprises a diuretic.

13. Pharmaceutical composition according to claim 12, characterised in that the diuretic is indapamide.